# Summary

This experiment successfully produced risperidone microspheres and evaluated the influence of key manufacturing parameters on their formation. A central finding was that a hybrid setup, combining manual pumps with automated washing, yielded more consistent droplet sizes (standard deviation ~12 µm) compared to a fully automated platform (~21 µm). Results indicated that increasing the continuous flow rate from 15 mL/min to 30 mL/min effectively reduced mean droplet size, whereas a further increase to 45 mL/min produced negligible change. Membrane size alterations did not significantly affect droplet size or dispersity. The investigation concluded that the hybrid setup enhances droplet consistency and that adjusting flow rate is an effective method for controlling droplet size. Future work will focus on exploring the impact of hardening time on microsphere properties.

# Introduction

The development of pharmaceutical formulations requires a thorough evaluation of their physical properties, performance, and stability. This project was initiated to produce risperidone microspheres and systematically investigate how process parameters influence their final characteristics. The motivation was to generate microspheres of various sizes to assess the impact of size blending on drug release rates. The experiment attempted to control microsphere size and consistency by manipulating manufacturing variables, including the level of automation (a fully automated platform versus a hybrid setup), continuous flow rate, membrane size, and the duration of dilution and recirculation hardening times.

# Objectives

The project had the following objectives:

1. To produce risperidone microspheres of various sizes using an automated platform.

2. To evaluate the effect of continuous flow rates (15, 30, and 45 mL/min) and membrane sizes (10x200 and 20x200) on microsphere size and consistency.

3. To compare the consistency of formulations produced by a fully automated setup versus a hybrid setup.

4. To investigate the effects of varying hardening times (6, 12, and 18 minutes) on microsphere formation.

# Methodology

## Methodology

## Microsphere Fabrication for Size Control

Risperidone microspheres were fabricated to investigate the effects of process parameters on particle size. Formulations were prepared in triplicate to ensure sufficient yield for analysis. Two distinct manufacturing configurations were evaluated: a fully automated platform and a hybrid system. The hybrid setup utilized manual axial flow (AXF) pumps for emulsification, followed by automated tangential flow filtration (TFF) for washing. Within each configuration, two process variables were systematically altered. The continuous phase flow rate was set to 15 mL/min, 30 mL/min, or 45 mL/min. Concurrently, two membrane sizes, 10x200 and 20x200, were used to modulate microsphere formation. The primary objective of this approach was to generate microspheres of varying sizes to assess their potential for creating blended samples with tailored release profiles.

## Evaluation of Hardening Time

A separate experiment was conducted to determine the effect of hardening time on microsphere properties using the automated platform. A single risperidone formulation was prepared in triplicate for this study. The key variable was the time elapsed between the addition of the formulation to the beaker and the initiation of TFF recirculation, defined as the "hardening time." This duration was systematically increased across the triplicate runs, with hardening times of 6, 12, and 18 minutes being tested. This study aimed to understand the impact of dilution and recirculation timing on microspheres produced via the automated system.

## Microsphere Size Characterization

Following fabrication, all microsphere samples were analyzed to determine their particle size characteristics. The key parameters measured for each sample were the mean and median droplet size, as well as the standard deviation of the size distribution, which served as a measure of sample dispersity `[FIGURE\_1]`.

\*\*Figure 1: Droplet size and distribution data for risperidone microspheres fabricated under varying process conditions.\*\*

# Results

\*\*Results\*\*

## Effect of Manufacturing Parameters on Droplet and Microsphere Characteristics

The impact of different manufacturing parameters on risperidone microsphere formation was evaluated by measuring droplet size and distribution. Two primary manufacturing setups were compared: a fully automated platform ("autobuild") and a hybrid process involving manual AXF pumps followed by automated TFF washing ("hybrid"). The hybrid build setup produced formulations with greater droplet size consistency, exhibiting a standard deviation (SD) of approximately 12 µm, compared to approximately 21 µm for the autobuild platform. The mean droplet sizes within triplicate batches were also more tightly grouped in the hybrid builds.

The influence of the continuous phase flow rate was tested at 15, 30, and 45 mL/min. For both build setups, increasing the flow rate resulted in a decrease in the mean and median droplet size and a reduction in the size distribution SD. A pronounced drop in size and SD was observed when the flow rate was increased from 15 mL/min to 30 mL/min, while the change from 30 mL/min to 45 mL/min was less substantial. Representative images of the initial emulsion droplets are shown in `[FIGURE 1]`. Several formulations (RI43, RI44, RI45) were observed to form a slurry.

\*\*Figure 1: Representative microscopy images of risperidone emulsion droplets (e.g., RI25-RI38) formed under varied process conditions. Samples RI43, RI44, and RI45 were noted as having a slurry-like appearance.\*\*

The effect of membrane size was assessed using both 10x200 and 20x200 membranes. No significant, consistent change in droplet size or dispersity was observed when changing the membrane size. Within the autobuild formulations, the 10x200 membrane produced droplets with a lower SD at slower speeds but a higher SD at faster speeds. In the hybrid setup, the 10x200 membrane yielded comparable or slightly higher SDs and a larger average droplet size than the 20x200 membrane. The morphology of the final, post-lyophilization particles is shown in `[FIGURE 2]`.

\*\*Figure 2: Representative images of risperidone microspheres post-lyophilization (e.g., RI25\_PL-RI38\_PL), showing the final particle morphology.\*\*

## Most Impactful Features

\* \*\*Build Setup\*\* — The hybrid process produced more uniform droplets (SD ~12 µm) compared to the fully automated process (SD ~21 µm), indicating that the manual AXF step allowed for more controlled emulsification.

\* \*\*Continuous Phase Flow Rate\*\* — Increasing the flow rate from 15 to 45 mL/min decreased the mean droplet size and narrowed the size distribution. Higher shear forces generated at increased flow rates result in the formation of smaller droplets.

\* \*\*Membrane Size\*\* — Altering the membrane size from 20x200 to 10x200 did not produce a meaningful or predictable impact on droplet size or dispersity, suggesting that flow rate was the dominant parameter for size control in this system.

## Evaluation of Microsphere Hardening Time

An experiment was conducted on the automated platform to assess the effect of hardening time on microsphere properties. Using a consistent formulation prepared in triplicate, the time between the initial formulation addition and the start of TFF recirculation was varied at 6, 12, and 18 minutes. The results for these experimental cohorts were not available for this report.

# Conclusion

This study successfully demonstrated that risperidone microsphere size can be controlled by modulating specific process parameters. The primary finding is that increasing the continuous phase flow rate effectively reduces the average and median droplet size. This effect was most pronounced when increasing the rate from 15 mL/min to 30 mL/min, with diminishing returns observed at 45 mL/min. Furthermore, a hybrid manufacturing setup, utilizing manual AXF pumps followed by automated TFF washing, yielded more consistent formulations with a lower standard deviation in droplet size distribution compared to the fully automated platform. Conversely, altering the membrane size from 20x200 to 10x200 did not produce a significant change in either droplet size or dispersity. These results indicate that flow rate is a key control parameter for tuning microsphere size, and the hybrid process offers superior batch consistency.